

Tuberous sclerosis complex in flies too? A fly homolog to TSC2, called gigas, plays a role in cell cycle regulation

Created: July 27, 2000

Tuberous sclerosis complex (TSC) affects as many as 1 in 6000 newborns. Although named in 1880 for the firm, potato-like nodules that form in the cerebral cortex, few organs escape the benign tumors called hamartomas that also sprout in the kidneys, lungs, heart, eyes, and skin. The first clinical signs of TSC include seizures, mental retardation, and skin lesions. However, symptoms can be so subtle that they go undetected for many years.

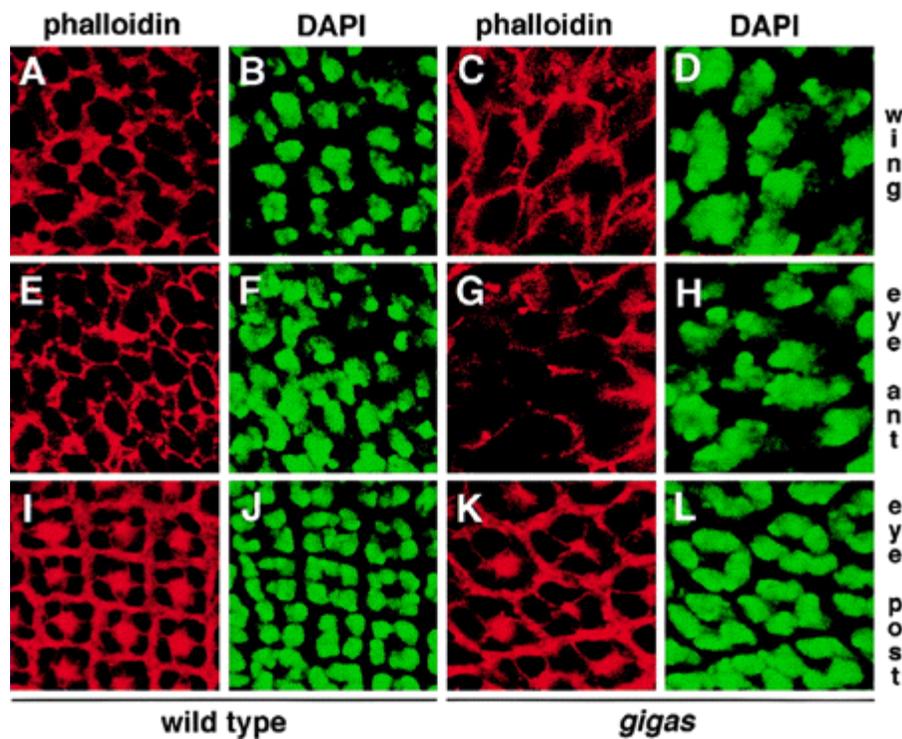
One-third of TSC patients inherit a defective copy of either the *TSC1* gene (chromosome 9q34) or the *TSC2* gene (chromosome 16p13.3). The remaining two-thirds acquire the disease by spontaneous mutation of either gene, probably very early in embryonic development. Because no individual lacking functional copies of both genes has ever been found, it is believed that such a condition is lethal to the embryo.

The product of the *TSC1* gene, hamartin, shows no overall sequence similarity to any known protein, although it contains an extensive coiled-coil region near its carboxyl end. Coiled-coil domains often provide a binding surface for protein-protein interactions. The *TSC2* product, tuberlin, is also novel but shows homology to the GTPase-activating protein (GAP) for Rap1 protein, a Ras superfamily member. Rap1's cellular function is not known, however, many Ras-related proteins help to pass stimulatory signals, from the plasma membrane to the nucleus, that tell a cell when to divide. The GTP-dependent proteins within these signaling cascades can only

transmit a signal when in a GTP-bound state. The role of the GAP is to inactivate the signaling protein by hydrolyzing its bound GTP to GDP. GAPs are therefore critical negative regulators of the Ras-like proteins and thus prevent cells from dividing unchecked.

The discovery last year of *TSC1* and *TSC2* homologs in *Drosophila* strengthens the idea that they are fundamental to cell division control. Mutant flies lacking tuberlin possess enlarged cells that contain on average ten times the normal amount of DNA, indicating that the cells repeatedly replicated their DNA without going through intervening cell divisions. A similar process may explain the giant, multinucleated cells seen in certain neuronal tumors of TSC patients. In addition, experiments in human cells have shown that when tuberlin protein levels are reduced, the cells prematurely enter the cell division cycle.

What about hamartin? It may be telling that *TSC1* patients are clinically indistinguishable from *TSC2* patients. One idea is that tuberlin and hamartin bind to each other in cells, facilitated by hamartin's coiled-coil domain. Perhaps hamartin is there to keep tuberlin fully active, or the tuberlin-hamartin complex itself is the functional tumor suppressor. Although the precise cellular actions of tuberlin and hamartin remain to be discovered, the strongly homologous proteins found in *Drosophila* offer the potential for further experimental investigation.



In *Drosophila*, the *gigas* gene codes for a protein homologous to human *TSC2*. Fly cells from the wing and eye imaginal discs that contain mutant *gigas* are enlarged, suggesting that the cells failed to undergo cell division at the appropriate time. The figure shows confocal images of DNA-stained (green; DAPI) and phalloidin-stained (red — phalloidin is a toxin that tightly binds actin) wild-type (left-most two columns) and mutant (right-most two columns) cells. (A-D) are wing disc cells, (E-H) are cells from the eye disc anterior to the morphogenetic furrow (MF), while (I-L) are from the eye disc posterior to the MF. The red actin stain shows that the size of the whole cell increases in mutant cells, while the green DNA stain shows that the size of the nucleus also increases in mutant cells.

Important Links

Live PubMed searches

- (1) TSC in flies
- (2) Autosomal dominant TSC
- (3) REVIEWS

Additional NCBI resources

- TSC1 in OMIM
- TSC2 in OMIM
- TSC in LocusLink [<http://www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=TSC1+or+TSC2>]

Box: Search PubMed for the outcomes of surgery

Click on the link below to start an html tutorial.

Outcomes of surgery for TSC [http://www.ncbi.nlm.nih.gov/Coffeebreak/CB15_gigas/PQ.html]

Box: Use BLAST to search for proteins similar to human TSC2

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Search for proteins similar to human TSC2 [http://www.ncbi.nlm.nih.gov/Coffeebreak/CB15_gigas/BQ.html]